Morgan, Lewis & Bockius LLP
1111 Pennsylvania Avenue, NW
Washington, DC 20004
Tel: 202.739.3000
Fax: 202.739.3001
www.morganlewis.com

Morgan Lewis
COUNSELORS AT LAW

Kathleen M. Sanzo
202-739-5209
ksanzo@morganlewis.com

May 13, 2004

VIA OVERNIGHT MAIL

Dockets Management Branch
Food and Drug Administration
Department of Health and Human Services
Room 1061, HFA-305
5630 Fishers Lane
Rockville, MD 20857

Re: CITIZEN PETITION

Dear Madam or Sir:

Pfizer Inc ("Pfizer") submits the attached Citizen Petition under 21 C.F.R. § 10.30, requesting rejection by the Food and Drug Administration of New Drug Application 21-426 for OMNITROP™ 5.8 mg somatropin [rDNA origin] for injection, lyophilized powder and diluent with preservative, filed by Biochemie U.S., Inc. and Sandoz, Inc.

Sincerely,

Kathleen M. Sanzo

Kathleen M. Sanzo
Counsel for Pfizer Inc

Attachments

2004P-0231

CP1

cc: Jeffrey B. Chasnow, Esq.
Arnold I. Friede, Esq.
David S. Smith, Esq.
Stephen Paul Mahinka, Esq.
Dr. Phoebe Mounts, Esq.
Lawrence S. Ganslaw, Esq.

Morgan Lewis
COUNSELORS AT LAW

Pfizer Inc

CITIZEN PETITION REQUESTING

FDA REJECTION OF OMNITROP™

May 13, 2004

Of Counsel:

Jeffrey B. Chasnow, Esq.
Arnold I. Friede, Esq.
David S. Smith, Esq.
Pfizer Inc

Submitted By:

Kathleen M. Sanzo, Esq.
Stephen Paul Mahinka, Esq.
Dr. Phoebe Mounts, Esq.
Lawrence S. Ganslaw, Esq.
Morgan, Lewis & Bockius, LLP
Counsel for Pfizer Inc

TABLE OF CONTENTS

Table of Contents

Pfizer Inc ("Pfizer") submits this petition under 21 C.F.R. § 10.30 to request that the Food and Drug Administration ("FDA" or "the Agency") immediately deny approval of New Drug Application ("NDA") 21-426 for OMNITROP™ 5.8 mg somatropin [rDNA origin] for injection, lyophilized powder and diluent with preservative,[1/] filed by Biochemie U.S., Inc. and Sandoz, Inc. ("Sandoz") under Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act ("FFDCA"). Regardless, Omnitrop™ should not be "A" rated.[2/]

I. Actions Requested

Pfizer requests that FDA immediately deny approval of NDA 21-426 because:

- It is scientifically and legally improper for FDA to rely on, reference, or otherwise use the clinical and manufacturing information establishing the safety and effectiveness of GENOTROPIN® (somatropin [rDNA origin] for injection) to approve Omnitrop™; and

- The Omnitrop™ data do not adequately address the safety, effectiveness and manufacturing considerations for recombinant human growth hormone ("rhGH") products or the specific product differences between Genotropin® and Omnitrop™.

II. Statement of Grounds

A. Summary

Sandoz filed a section 505(b)(2) application for Omnitrop™, rather than a full NDA (i.e., a section 505(b)(1) application), in order to forego certain significant analytical and clinical testing and other requirements, and instead rely on the proprietary information submitted by Pfizer for Genotropin®. There are legal and scientific reasons why FDA can not approve Omnitrop™ on this basis.

Genotropin® is a highly complex recombinant protein manufactured by an inherently complex biosynthetic process, and like other innovator rhGH products, its characterization by physical and chemical tests is complicated by the presence of molecular variants and other impurities. Consequently, the only way for FDA to determine the similarity of the Omnitrop™

1/ Sandoz' notice of patent certification to Pfizer refers to this product as "OMNITROPE™," but all other available documents refer to the product as "OMNITROP™." For convenience, the product is referred to as "Omnitrop™" in this citizen petition, and refers to the product that is the subject of NDA 21-426.

2/ The attachments to this citizen petition, as required by 21 C.F.R. § 10.20(c), are organized into two volumes: (1) Volume I contains all referenced peer-reviewed scientific articles, scientific abstracts, and other scientific materials, ordered alphabetically by the last name of the first author (or in the case of an institutional author, by institution name); and (2) Volume II contains all other referenced documents required to be submitted to FDA. The citizen petition references for the Volume I materials do not include attachment numbers (as they are provided in alphabetical order by author name), while the references for the Volume II materials do include attachment numbers.

structure and characteristics would be for the Agency to reference the non-public, proprietary chemistry, manufacturing, and control ("CMC") information in the Genotropin® NDA and supplements. As explained at length in previous citizen petitions and court proceedings, which are incorporated by reference,[3/] FDA's reliance on or use of proprietary data to evaluate the Omnitrop™ section 505(b)(2) application violates legal requirements, including the FFDCA, the Administrative Procedure Act ("APA"), and the Trade Secrets Act. Accordingly, in order for FDA to use the Genotropin® information to support the approval of Omnitrop™, the Agency would need to rely on Pfizer's non-public, proprietary data, but that is prohibited by law.

Even if FDA legally could rely on Pfizer's proprietary data to approve Omnitrop™, Genotropin® and Omnitrop™ have so many important chemical and formulation differences—including molecular weight, genetic sequence of the recombinant plasmid, master and working cell banks, and preservatives—that FDA can not make a scientifically-rational decision about the safety and effectiveness of Omnitrop™ based on the proprietary Pfizer data, limited public Genotropin® data, and publicly available Sandoz data. Consequently, absent additional testing and data on Omnitrop™, FDA will not be able to confirm the batch-to-batch reproducibility, stability, level of adverse events, dosing, and overall safety and effectiveness of this proposed product.

For nearly 20 years, several safe and effective rhGH products have been available in the U.S. because FDA has required full reports of indication-specific clinical trials, pre-clinical data, and CMC information to establish their safety and effectiveness. As it is legally and scientifically improper for FDA to approve Omnitrop™ on the basis of the proprietary or public Genotropin® information, the Agency's approval of the Omnitrop™ 505(b)(2) application would simply lower the rigorous approval standards that historically have served well the many thousands of children and adults who have used rhGH products, in a market context where there are already several alternative products. Because Pfizer has significant concerns about lowering the approval standards for rhGH products, and the potential for approval of an inferior product as compared to Genotropin®, Pfizer has sought to intervene in proceedings before the European Court of First Instance to support the European Commission's refusal to grant approval for Omnitrop™ (in

---

3/ Pfizer Inc. v. Food and Drug Admin., No. 1:03CV02346 (D.D.C. filed Nov. 13, 2003) (Volume II, Attach. 1) (Pfizer challenge to FDA approval of Dr. Reddy's Laboratories, Inc./Dr. Reddy's Laboratories, Ltd. ("Reddy's") Section 505(b)(2) application for amlodipine maleate, and FDA's policy concerning its asserted authority to rely on its general findings of safety and efficacy from NDAs to approve section 505(b)(2) applications); Citizen Petition filed on behalf of Genentech, Inc., No 2004P-0171 (filed April 8, 2004) (see note 12 concerning the different and inconsistent terminology used in this petition); Citizen Petition filed on behalf of the Biotechnology Industry Organization, No. 01P-0323 (filed April 23, 2003); Citizen Petition filed on behalf of Pfizer, Inc., No. 2002P-0447 (filed Oct. 11, 2002); Pfizer's/Pharmacia's Response to Comments Submitted by the Generic Pharmaceutical Association (GP*h*A) and Amendment to Citizen Petition, No. 01P-0323 (Apr. 4, 2002); Comments of Abbott Laboratories, No. 01P-0323 (July 10, 2002); Comments of Bristol-Myers Squibb Company, No. 01P-0323 (July 15, 2002); Citizen Petition filed on behalf of Pfizer, Inc. and Pharmacia Corporation, No. 01P-0323 (filed July 27, 2001).

reliance on reports of studies for other rhGH preparations and limited comparative studies with Genotropin®).[4/]

Regardless of whether FDA approves the Omnitrop™ section 505(b)(2) application, the Agency legally and scientifically can not determine that Genotropin® and Omnitrop™ are pharmaceutically- or bio-equivalent, and Omnitrop™ therefore can not be assigned an "A" therapeutic equivalence rating.

B. Background

1. Patients Require a Safe and Effective Genotropin®

Genotropin® (somatropin [rDNA origin] for injection), the second growth hormone product on the U.S. market, has been marketed for 17 years as a safe and effective therapy for growth hormone deficiency in children and adults. The availability of Genotropin® and other rhGH products has resulted in the widespread use of rhGH as growth hormone replacement therapy. Consequently, the public health ramifications of FDA approval of an unsafe or ineffective rhGH, potentially such as Omnitrop™, are significant. Hundreds of thousands of children and adults use GH over prolonged periods, including over a whole lifetime, and the use of an unsafe and/or ineffective product could result in permanent adverse health effects for these patients. Pediatric patients would suffer the greatest potential losses.

While the approval of an unsafe rhGH product is unacceptable given the long-standing availability of multiple safe rhGH products, the consequences of a less effective rhGH will also be detrimental. If children with growth hormone deficiency ("GHD") receive less effective or ineffective product especially during early treatment, they likely will never reclaim the growth they lose as a result of the product's ineffectiveness.[5/] The result of using a less effective or ineffective product is, therefore, equivalent to a delay in or loss of therapy—a lost opportunity that may be impossible to regain. Thus, it is incumbent on FDA to require that all rhGH applicants demonstrate the safety and effectiveness of their products through full reports of rigorous, population-specific clinical testing and manufacturing processes. Moreover, in view of the availability of multiple safe and effective rhGH products, there is no necessity or economic basis for approving an application which cannot fully stand on its own scientific merits.

4/ See Case T-15/04, Sandoz GmbH v. Commission of the European Communities, 2004 OJ C71/35, 20.3.2004 (Annex 1) (Volume II, Attach. 2).

5/ E.g., M.B. Ranke et al., 1999. Derivation and Validation of a Mathematical Model for Predicting the Response to Exogenous Recombinant Human Growth Hormone (GH) in Prepubertal Children with Idiopathic GH Deficiency. Journal of Clinical Endocrinology and Metabolism 84:1174-1183 (showing that a variable for predicting second, third, and fourth year growth responses is height velocity during the previous year); L. Wetterau and P. Cohen, 2000. New Paradigms for Growth Hormone Therapy in Children. Hormone Research 53 (Supp. 3):31-36 (stating that it is well established that GH should be initiated as early as possible in the child with GHD to optimize final height outcome).

2. *There are Important Differences Between Genotropin® and Omnitrop™*

In addition to the legal bases that preclude FDA from relying on Pfizer's proprietary data, there are important differences between Genotropin® and Omnitrop™ that preclude reliance on any Genotropin® data or findings of safety and effectiveness. First, there is a significant difference in the reported molecular weights of the somatropin, or rhGH, of the two products. The molecular weight of the somatropin in Genotropin® (191 amino acids) is 22,124 daltons,[6/] while the molecular weight of the somatropin in Omnitrop™ (191 amino acids) is 21,125 daltons.[7/] This difference is in comparison to the theoretical molecular weight of rhGH that is reported to be 22,125 daltons (191 amino acids).[8/] The molecular weight of many of the rhGH products approved by FDA is 22,125 daltons (191 amino acids).[9/] Thus, the active pharmaceutical ingredients in Genotropin® and Omnitrop™ are different chemically.

The chemical basis for the differences in the molecular weights between Genotropin® and Omnitrop™ has not been established, but is likely due to differences in the manufacturing processes. Accordingly, as explained below, it is scientifically improper for FDA to rely on, reference, or use CMC documentation and clinical data establishing the safety and effectiveness of Genotropin® to approve Omnitrop™.

Second, there also significant differences in the formulation of Genotropin® compared to Omnitrop™, including the lyophilized drug powder, and the preservative in the diluent used to reconstitute the product for injection. Mannitol is present in the drug powder and diluent of Genotropin®, but not for Omnitrop™—Pfizer has proprietary data demonstrating the importance of mannitol to product characteristics, including stability. The preservatives in the diluents are also different for the two products. Genotropin® contains m-cresol, and Omnitrop™ contains benzyl alcohol. These and other formulation differences, which are discussed below, can significantly affect the quality and safety of Omnitrop™.

Third, the scope and amount of available information and data concerning Omnitrop™, including clinical studies, are markedly smaller and narrower than the clinical studies and worldwide experience with Genotropin® over the past 17 years. As discussed below, Sandoz has conducted only limited studies of Omnitrop™ that fail to address adequately the recognized safety and effectiveness considerations for rhGH products, and fail to address the impact of the

---

6/ Package Insert, GENOTROPIN®, somatropin (rDNA origin) (2004) (Volume II, Attach. 3).

7/ Biochemie GmbH, Study Protocol, An Open, Multicentre Phase III Study To Demonstrate The Efficacy and Safety of Omnitrop™ Lyophilised (Somatropin) in the Treatment of Growth-Deficient Children Due to Insufficient Endogenous Growth Hormone Secretion (10.02.2002), at 3 (Volume II, Attach. 4).

8/ European Pharmacopoeia 3rd ed. – Supplement, 1999. Somatropin (1999:0951), Somatropin Bulk Solution (1999:0950), Somatropin for Injection (1999:0952).

9/ For example, Genentech's Nutropin®, Eli Lilly's Humatrope®, and Serono Laboratories' Saizen® all have molecular weights of 22,125 (191 amino acids). The molecular weight of Novo Nordisk Pharmaceuticals' Norditropin® is 22,000 (191 amino acids).

significant differences between Omnitrop™ and Genotropin®. The limited Sandoz studies are inadequate, in part, because they concern at least two different versions of Omnitrop™. After the only known comparative trial between Omnitrop™ and Genotropin®, Sandoz changed its manufacturing process for Omnitrop™ through the addition of several purification steps to remove high concentrations of *E. coli* host cell peptides. Consequently, Sandoz apparently has not compared the safety and effectiveness of its final Omnitrop™ product with Genotropin®. Thus, only a portion of Sandoz' clinical testing is even applicable to review by FDA of the final Omnitrop™ product. Moreover, Sandoz has only conducted one now irrelevant comparative study with Genotropin®, and FDA ordinarily requires two clinical studies in order to establish comparable effectiveness between two products.

C. Argument

1. FDA Cannot Approve Omnitrop™ as a Matter of Law

Section 505(b) of the FFDCA and FDA's regulations and guidelines concerning the approval of NDAs, including Section 505(b)(2) applications, require that NDA applicants submit full reports of investigations to demonstrate that the drug is safe and effective for use. Moreover, pursuant to section 505(d) of the FFDCA, FDA must deny approval of an NDA if "the investigations, reports of which are required to be submitted to [FDA] pursuant to subsection (b) of this section, do not include adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof ...."[10/] Pfizer has previously asserted that FDA's reliance on or use of proprietary data to evaluate a section 505(b)(2) application such as that for Omnitrop™ violates, among other requirements, the FFDCA, the APA, and the Trade Secrets Act.[11/]

Recombinant proteins such as Genotropin® have extremely complex structures and characteristics, such that the only way to potentially evaluate the similarity of follow-on products would be on the basis of detailed CMC information in the innovator NDA.[12/] The CMC information for Genotropin® is not in the public domain, and is proprietary trade secret information. Consequently, the only way theoretically to approve a follow-on recombinant protein

---

10/ 21 U.S.C. § 355(d)(1).

11/ See supra note 3 and accompanying text.

12/ This citizen petition uses the terms "follow-on version" or "follow-on product" to refer to products purported to be similar to innovator products that are approved on the basis of less than full, independent reports of safety and effectiveness. In a citizen petition filed on April 8, 2004, Genentech ascribed a different definition to the term "follow-on" which is inconsistent with Pfizer's use of this term. Citizen Petition filed on behalf of Genentech, No. 2004P-0171 (filed April 8, 2004). Whatever the nomenclature used, Pfizer's position is that recombinant protein products, including rhGHs, are unique and defined by their manufacturing process, such that they can not be determined by the Agency to be comparable to one another.

product would be in reliance on or through use of this proprietary data, which is prohibited by law.[13/]

For example, as explained further in Section II.C.7.a. of this petition, in order to determine whether Genotropin® and Omnitrop™ are sufficiently similar such that the Agency theoretically could rely on or use the Genotropin® information to support the approval of Omnitrop™, FDA would need to examine Pfizer's non-public, proprietary data in the Genotropin® NDA and NDA supplements, or prior FDA findings based on such data (collectively "NDA for Genotropin®").

More specifically, FDA would need to compare, among other factors, the products' recombinant plasmids, master cell banks, and working cell banks. Both the sequence of the recombinant plasmid used to manufacture Genotropin®, and the Genotropin® characterization information necessary to ascertain the impact of variations in the master and working cell banks, however, are proprietary. FDA is prohibited by law from examining or otherwise using the NDA for Genotropin® for this purpose. Consequently, because FDA is legally prohibited from accessing the very data it needs to determine whether Genotropin® and Omnitrop™ are similar, the Agency simply cannot engage in reasoned decisionmaking as required under the APA with respect to Omnitrop™.[14/] As such, it would be both inequitable and raise public health concerns for the Agency to evaluate Omnitrop™ without access to complete independent information about its safety and effectiveness. These concerns have been manifested with drugs and biologics previously approved notwithstanding inadequate product comparisons, which only become clear post-approval.[15/]

13/ FDA reliance on Pfizer's proprietary and trade secret CMC data would squarely be at odds with the United States government's policy on international recognition and protection of intellectual property rights, to foster innovation and protect investment-backed expectations. See, e.g., United States U.S. Statement on Intellectual Property and Access to Medicines at the June 20 TRIPS Council Meeting available at http://www.ustr.gov/sectors/speech01.PDF (last visited May 12, 2004) (Volume II, Attach. 5). See also, United States Trade Representative, 2004 Special 301 Report, Executive Summary 4 (2004) (Volume II, Attach. 6) (citing Article 39.3 of TRIPS Agreement, that requires WTO members to protect test data submitted by drug companies to health authorities against disclosure and "unfair commercial use," a key implementation priority for 2004). Further, FDA itself has sought to ensure the protection of proprietary information in its dealings with foreign governments. See, F-D-C Reports, Inc., "The Pink Sheet" 66(1):22 (Jan. 5, 2004). FDA/EU Agreement Calls for Sharing of GMP and Postmarketing Data (Volume II, Attach. 7).

14/ In determining whether an agency's actions are arbitrary and capricious under the APA, the courts have held that the principal inquiry is whether an agency's action constitutes "reasoned decisionmaking." See, e.g., American Lung Ass'n v. EPA, 134 F.3d 388, 392 (D.C. Cir. 1998) ("we have always required the Administrator to 'cogently explain why [she] has exercised [her] discretion in a given manner'") (quoting Motor Vehicle Mfrs. Ass'n v. State Farm Mut. Auto. Ins. Co., 463 U.S. 29, 48 (1983)); Milk Indus. Found. v. Glickman, 967 F. Supp. 564, 570 (D.D.C. 1997) (reasoned decisionmaking precludes "a '[s]udden and unexplained change'") (quoting Smiley v. Citibank, 517 U.S. 735, 742 (1996)).

15/ E.g., Letter from Professor Alasdair Breckenridge, Chairman of Committee on Safety of Medicines (UK), to Medical Directors of NHS Trusts, Eprex (epoetin alfa) and Pure Red Cell Aplasia – (Continued)

2. The Public Omnitrop™ Data are Insufficient to Support its Approval

The publicly available Omnitrop™ data are inadequate to independently establish Omnitrop™'s safety or effectiveness, or to account for the formulation, manufacturing, and packaging differences between Omnitrop™ and Genotropin®.

Sandoz has already had significant Omnitrop™ manufacturing process problems with clinical consequences, including the development of anti-GH antibodies at much higher levels than for approved rhGH formulations such as Genotropin®.[16/] The fact that Omnitrop™ has been shown to be more antigenic than Genotropin® raises fundamental concerns about the Sandoz process, and evidences the risks associated with a de novo rhGH manufacturing process. Moreover, because the only known comparative trial conducted between Omnitrop™ and Genotropin® was conducted prior to changes in Omnitrop™'s manufacturing process—intended to remove the higher concentrations of *E. coli* host cell peptides—that testing is no longer relevant to establishing the similarity of the two products, because changes in manufacturing method can induce changes in stability and structure of the rhGH molecule. In view of this deficiency, Sandoz apparently has conducted no comparative study between the final Omnitrop™ product and Genotropin®, and cannot meet FDA's requirements for two controlled clinical studies to demonstrate comparable effectiveness between two products.

Moreover, the clinical testing for Omnitrop™ has only been conducted in children with GHD, and not adults with GHD, children with Prader-Willi Syndrome, and children born small for gestational age who fail to manifest catch-up growth, for which Pfizer has demonstrated the safety and effectiveness of Genotropin®. For the many reasons documented in this citizen petition, rhGH products can only be approved on the basis of full, independent, indication-specific clinical trials. Consequently, approval of Omnitrop™ for indications not supported by independent, indication-specific clinical trials, now or in the future after expiration of exclusivity, is not scientifically supportable.[17/]

Contraindication of Subcutaneous Administration to Patients with Chronic Renal Disease (Dec. 12, 2002) available at http://www.info.doh.gov.uk/doh/embroadcast.nsf/ vwDiscussionAll (last visited May 12, 2004) (Volume II, Attach. 8) (reporting 155 case reports of pure red cell aplasia ("PRCA") confirmed by bone marrow biopsy world-wide; of these, 112 reports had documented presence of anti-erythropoietin antibodies); F-D-C- Reports, Inc., "The Pink Sheet" 66(19):4 (May 10, 2004) (Volume II, Attach. 9) (quoting CDER Acting Director Dr. Steven Galson as stating, "It is currently not really scientifically possible to establish that two proteins are exactly the same ... I think those of you that follow erythropoietin know that issue."); F-D-C- Reports, Inc., "The Pink Sheet" 62(43):16 (Oct. 23, 2000) (Volume II, Attach. 10) (reporting that SangStat recalled and discontinued SangCya after discovering that this product was not bioequivalent to Neoral (cyclosporine) oral solution when mixed with apple juice as recommended in the labeling).

16/ F. Peter et al. Long-Term (21 Months) Efficacy and Safety of New Liquid Recombinant Human Growth Hormone (Omnitrop™ Solution for Injection) in Pretreated Short Children with Growth Hormone Deficiency. (The year and publication of this abstract are unknown).

17/ To the extent that Sandoz intends to rely on clinical studies that have scientific merit—and Sandoz can overcome the numerous other legal and scientific obstacles to approval described in this Citizen (Continued)

Sandoz apparently has also failed to conducted adequate pre-clinical studies of Omnitrop™, including suitable pharmacological and toxicological testing in animals and cell lines, as well as Phase II dosing studies, the latter being essential in view of the differences in the drug delivery systems for Genotropin® and Omnitrop™.

3. Genotropin® and Omnitrop™ are Too Different to Support Even Improper FDA Reliance on Pfizer's Data

Because Genotropin® and Omnitrop™ have chemically different active ingredients and formulations, it is scientifically improper and inadequate for FDA to rely on or use as support for approval of Omnitrop™ either the proprietary or public pre-clinical, clinical, and CMC information establishing the safety and effectiveness of Genotropin®. More specifically, as explained further in Section II.C.7. of this petition, Genotropin® and Omnitrop™ have different molecular weights, genetic sequences of the recombinant plasmid, master and working cell banks, preservatives, containers, reconstitution procedures, and delivery systems/dosing, which are important chemical and formulation differences. As summarized above, the public information about Omnitrop™ indicates that Sandoz has not compiled adequate pre-clinical data, conducted Phase II dosing studies, or conducted adequate Phase III studies for this proposed product. Without such information and data, FDA will not be able to confirm the batch-to-batch reproducibility, stability, level of adverse events, dosing, and overall safety and effectiveness of Omnitrop™.

Moreover, approval of Omnitrop™ would be arbitrary and capricious given the requirements FDA has imposed on the Genotropin® manufacturing process. Consistent with the rigorous scientific standards and current Good Manufacturing Practice ("cGMP") requirements for manufacturing safe and effective recombinant proteins, Pfizer has carefully evaluated and conducted appropriate analyses and studies to establish and make incremental changes to the Genotropin® manufacturing process.[18/] In making specific, discrete changes to its process, Pfizer has utilized both proprietary in-process and final product assays and reagents, and significant historical proprietary pre-clinical and clinical safety and effectiveness data. The NDA for Genotropin® includes a digest of this information, but does not include the full complement of documentation Pfizer uses to evaluate process changes.

Petition—as a legal matter, the FFDCA nevertheless limits any approval to the specific indications fully supported by Sandoz' trials. That is because section 505(b)(2) of the FFDCA incorporates section 505(b)(1), which requires that the "investigations . . . show . . . such drug is effective *in use*." (emphasis added). In the absence of an indication-specific clinical trial, therefore, there is no investigation showing the drug to be effective "in use" for that particular indication.

18/ Sandoz' reliance on clinical studies to bolster its case for similarity between Omnitrop™ and Genotropin® is fundamentally at odds with the principle, embodied in FDA's cGMP regulations, that finished product testing is never a scientifically appropriate surrogate for adequate in-process controls. See, Citizen Petition filed on behalf of Genentech, Inc., No 2004P-0171 (filed April 8, 2004), at footnote 7. In other words, as a matter of science, law, and policy, Sandoz should not be permitted to shore up the absence of front-end analyses and testing that FDA can lawfully rely upon to show Omnitrop™ and Genotropin® to be similar by advancing limited "back end" clinical studies of questionable merit.

In contrast, Sandoz has necessarily established a de novo manufacturing process for Omnitrop™, using new and different assays than that for Genotropin®. That is, as opposed to making measured, iterative changes to an established process, Sandoz has developed a wholly new manufacturing process for Omnitrop™ without access to or use of the Genotropin® in-process and final product assays or historical pre-clinical and clinical data. It would be impossible for Sandoz to duplicate Pfizer's Genotropin® manufacturing process unless it had access to the NDA for Genotropin®, which is prohibited by law. Nonetheless, Sandoz asserts in its section 505(b)(2) application that its product is safe and effective based exclusively on final product characteristics, despite the absence of adequate process information. Such an approval would be a dramatic reversal of longstanding FDA policy, and would be arbitrary and capricious in violation of the APA.

4. FDA Requires Extensive Pre-Clinical and Clinical Testing of Recombinant Proteins Such as Genotropin®

FDA and the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use[19/] ("ICH") recognize the need to consider specifically the manufacturing and toxicologic differences between recombinant proteins or "well-characterized, therapeutic, biotechnology-derived products,"[20/] with regard to their safety and effectiveness, and the need for clinical testing of these products. In discussing the acceptable limits and analytical methods used to ensure the identity, strength, quality, and purity of drug substances, FDA's Center for Drug Evaluation and Research ("CDER") and Center for Biologics Evaluation and Research ("CBER") have stated that:

> [v]alidation data and established specifications ordinarily need not be submitted at the initial stage of drug development. However, for some well-characterized, therapeutic biotechnology-derived products, preliminary specifications and additional validation data may be needed in certain circumstances to ensure safety in Phase 1.[21/]

19/ Like FDA guidance documents, ICH guidance "represents the agency's current thinking," and issuance of ICH guidance requires that American, European, and Japanese regulatory authorities agree on the scientific and technical issues addressed in the documents. Int'l Conference on Harmonisation, Guidance on General Considerations for Clinical Trials, 62 Fed. Reg. 66113, 66114 (Dec. 17, 1997).

20/ E.g., Food and Drug Admin., Guidance for Industry: Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-Derived Products (Nov. 1995); Int'l Conference on Harmonisation, Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products (Aug. 18, 1999).

21/ Food and Drug Admin., Guidance for Industry: Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-Derived Products 7 (Nov. 1995).

Similarly, CBER and CDER have stated that process and manufacturing process changes for proteins derived by recombinant DNA ("rDNA") technology "have a substantial potential to have an adverse effect on a product's identity, strength, quality, purity, or potency as they may relate to its safety or effectiveness."[22/] Examples cited by CBER and CDER of the kinds of changes that can have an adverse effect on the safety and effectiveness of the rDNA product include: changes in the purification process, such as a change in the sequence of processing steps or addition, deletion, or substitution of a process step; changes in the fermentor, bioreactor, or purification equipment; and changes of the site at which manufacturing is performed, which could affect contamination or cross-contamination precautions.[23/] The impact of changes in the manufacturing process is best understood by the manufacturer when release tests are coupled with controls on manufacturing history and extensive process validation during clinical use.

Recombinant DNA products have been viewed by FDA differently than synthetic drugs, with the Agency requiring different and/or additional tests to demonstrate safety and/or effectiveness because of difficulties in characterization and achieving purity. This is illustrated by the issues that may be addressed in end of Phase 2 meetings for protein products derived by rDNA technology, including:

> [a]dequacy of physicochemical and biological characterization (e.g., peptide map, amino acid sequence, disulfide linkages, higher order structure, glycosylation sites and structures, other post-translational modifications . . .); [b]ioassay (e.g., appropriateness of method, specificity, precision); . . . [r]emoval of product- and process-related impurities (e.g., misfolded proteins, aggregates, host cell proteins, nucleic acid); [b]ioactivity of product-related substances and product-related impurities relative to the desired product.[24/]

According to ICH guidance on general principles for the selection of test procedures and the setting and justification of acceptance criteria for proteins produced by rDNA technology, all specifications should be justified and not only linked to a manufacturing process, but also linked to preclinical and clinical studies.[25/] Consistent with this guidance, FDA properly should require a

---

22/ Food and Drug Admin., Guidance for Industry: Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Biological Products 3 (July 1997).

23/ Id. at 3-4. The scientific problems involved in the manufacturing process of biological products have also been cited by Dr. Kathryn C. Zoon, former Director of CBER, as having the potential to compromise the safety of the product. Food and Drug Admin., CBER Chief: Generic Biologics a Problem from Scientific Standpoint, FDA Week (Apr. 20, 2001).

24/ Food and Drug Admin., Draft Guidance for Industry: IND Meetings for Human Drugs and Biologics, Chemistry, Manufacturing, and Controls Information 8 (Feb. 2000).

25/ Int'l Conference on Harmonisation, Guidance on Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products, 64 Fed. Reg. 44928, 44932 (Aug. 18, 1999) (stating that "[s]pecifications are linked to a manufacturing process . . .[and] [s]pecifications are linked to preclinical and clinical studies").

(Continued)

manufacturer of a new rhGH product, such as Omnitrop™, to conduct extensive clinical testing, linked to adequate preclinical studies and a specific manufacturing process, to ensure product identity, strength, quality and purity.

Moreover, recombinant protein products, including rhGH, have historically been viewed by FDA as being defined principally by their product specifications and the process by which they are manufactured. That is because assays for process and product-related impurities in recombinant protein products do not necessarily provide absolute quantitative levels of specific impurities and are often measured against standards that are relatively heterogeneous and incompletely defined. Different analytical methods are required to determine purity, but this approach only provides relative measures of purity that are assay specific. As a consequence, FDA cannot establish comparability between products on the basis of quantity or quality of impurities or contaminants in them. Rather, FDA must evaluate comparability between products, such as Genotropin® and Omnitrop™, on the basis of the purification process for each product, and the impact on safety and effectiveness measured directly by clinical studies.

Importantly, existing FDA guidance concerning the comparability of therapeutic biotechnology-derived products[26/] is limited solely to changes in the same product within one company, or process-dependent changes.[27/] FDA has traditionally "examined proposed manufacturing changes on a case-by-case basis to determine the type of data, including clinical data, that were necessary to determine product comparability."[28/] Changing the manufacturer, the site, and the process are much more significant changes that necessitate full reports and extensive clinical data.

This point was also emphasized in the European Medicines Evaluation Agency ("EMEA") Committee for Proprietary Medicinal Products ("CPMP") guidance that advised "[w]hen a change in the manufacturing process results in modifying the specifications (drug substance/drug product) and/or in process controls, . . . appropriate pre-clinical and clinical studies could be considered as the only definite way to demonstrate comparability, at least for some specific features such as immunogenicity" (emphasis added). Comm. for Proprietary Medicinal Prods., European Medicines Evaluation Agency, Note for Guidance on Comparability of Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance 6 (Sept. 20, 2001) (Volume II, Attach. 11). The EMEA further stated that for a biotechnology-derived protein product claimed to be similar to another one already marketed, the situation represents "the most complicated case" and requires appropriate clinical studies, including "clinical trials demonstrating equal efficacy." Id. at 8; Comm. for Proprietary Medicinal Prods., European Medicines Evaluation Agency, Note for Guidance on Comparability of Medicinal Products Containing Biotechnology-Derived Proteins as Drug Substance: Annex on Non-Clinical and Clinical Considerations 7 (July 30, 2002) (Volume II, Attach. 12).

26/ Food and Drug Admin., Guidance Concerning Demonstration of Comparability of Human Biological Products, Including Therapeutic Biotechnology-Derived Products (April, 1996).

27/ Meeting of the Advisory Committee for Pharmaceutical Science (June 24, 1998) (quoting Dr. David Finbloom of FDA as saying the comparability document "is for the product within one company").

28/ Food and Drug Admin., Guidance Concerning Demonstration of Comparability of Human Biological Products, Including Therapeutic Biotechnology-Derived Products 3 (April, 1996).

5. *Follow-on Versions of Genotropin® Must be Supported by Clinical Trials That Adequately Address Safety*

The scientific literature identifies several specific issues that are critical to ensuring the safety and effectiveness of recombinant proteins, such as Omnitrop™.[29/] ICH guidance also recognizes that "[a]n inherent degree of structural heterogeneity occurs in proteins due to the biosynthetic processes used by living organisms to produce them . . . [and that] [h]eterogeneity can also be produced during manufacture and/or storage of the drug substance or drug product."[30/] For example, changes can occur in the plasmid that encodes the recombinant protein,[31/] and these changes are undetectable by analytical methods if the changes occur at a low frequency.[32/]

Moreover, analytical methods for determining purity of recombinant proteins are also limited in sensitivity and specificity, and can not distinguish between process- or product-related impurities, such as amino acid changes.[33/] The importance of even infrequent mutations, such as a single amino acid change in recombinant human growth hormone, derives from the fact that single amino acid changes have been shown to alter the immunogenicity of the protein, which can result in antibodies that decrease growth.[34/]

Because the mechanisms of antibody formation and the factors affecting this process are unknown, it is not possible to predict the potential of a particular form of rhGH to elicit antibody formation. Consequently, clinical studies are essential to determine whether these undetectable mutations significantly affect the safety and effectiveness of Omnitrop™.

29/ E.g., B. DiPaolo et al., 1999. Monitoring Impurities in Biopharmaceuticals Produced by Recombinant Technology. Pharmaceutical Science and Technology Today 2(2):70-82.

30/ Int'l Conference on Harmonisation, Guidance on Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products, 64 Fed. Reg. 44928, 44930 (Aug. 18, 1999).

31/ E.g., Food and Drug Admin., Biotechnology Inspection Guide Reference Materials and Training Aids 3 (Nov. 1991) (stating that "genetic stability of the cell bank during storage and propagation is a major concern").

32/ R.W. Shafer et al., 2000. Reproducibility of Human Immunodeficiency Virus Type 1 (HIV-1) Protease and Reverse Transcriptase Sequencing of Plasma Samples from Heavily Treated HIV-1 Infected Individuals. Journal of Virological Methods 86:143-153 (showing that as the proportion of the mutant in the population decreases from 50% to 5%, the sensitivity of detecting a mutation decreased from 88% to 30%). Another study measured the sequencing accuracy in mixtures with mutations and demonstrated that the mutant needed to be present at a level of 25% for 80% accuracy in detecting the mutation. T.D. Yager et al., 1999. High Performance DNA Sequencing, and the Detection of Mutations and Polymorphisms, on the Clipper Sequencer. Electrophoresis 20:1280-1300.

33/ B. DiPaolo et al., 1999. Monitoring Impurities in Biopharmaceuticals Produced by Recombinant Technology. Pharmaceutical Science and Technology Today 2(2):70-82.

34/ S.L. Kaplan et al., 1986. Clinical Studies With Recombinant-DNA-Derived Methionyl Human Growth Hormone in Growth Hormone Deficient Children. Lancet 1 (8483):697-700.

a. There is Potential for Adverse Immune Responses to Recombinant Proteins Such As Omnitrop™ From Molecular Variants and Host Cell Impurities

(i) *Adverse Immune Response to Therapeutic Recombinant Proteins Decreases Effectiveness and Safety*

Although not well understood, there are examples of allergic reactions to therapeutic recombinant proteins, such as hGH. For example, generalized urticaria from rhGH, Humatrope®[35] has been reported. When systemic allergic reactions, such as urticaria, occur, desensitization is necessary to continue treatment with GH replacement therapy,[36] because decrease in growth velocity has been found in children who develop antibodies that bind growth hormone.[37] The rate of antibody formation can not be predicted, and the number of patients developing antibodies varies depending on the rhGH product.[38]

Moreover, antibody formation against rhGH is not the only example of an immune response directed against a naturally-occurring protein when it is administered therapeutically as a recombinant protein. It is well recognized that rDNA biologicals can be immunogenic in human recipients, and that this immunogenicity is impossible to predict at this time.[39]

35/ S.B. Walker et al., 1992. Systemic Reaction to Human Growth Hormone Treated With Acute Desensitization. Pediatrics 90:108-109.

36/ Id.

37/ E.g., P. Pitukcheewanont et al., 2000. Resumption of Linear Growth after Nutropin® Therapy in a Patient with Neutralizing Anti-Growth Hormone Antibodies to Protropin®. Endocrine Society Meeting, Abstract 1986; R.D.G. Milner et al., 1979. Experience with Human Growth Hormone in Great Britain: The Report of the MRC Working Party. Clinical Endocrinology 11:15-38 (reporting that 31% of the patients who developed high affinity antibodies to hGH had disturbed growth patterns); W.K. Waldhäusl and F. Rath, 1971. Development of Antibodies to Human Growth Hormone (HGH) in Children of Short Stature Treated with HGH. Acta Endocrinologica 68:345-354 (reporting data to show that development of antibodies against hGH can result in the development of resistance to the therapeutic effect of hGH).

38/ For example, among 106 children receiving 0.3 to 0.6 mg/kg/week of Nutropin® by subcutaneous injection, no GH deficient children had antibodies at baseline, but 15% developed antibodies after six months. Genentech, Inc.'s Nutropin® New Drug Application NDA 19-676, Study 86-061, entitled "A Phase III Multiclinic, Prospective Open-Label Randomized Study of Nutropin® (somatropin for injection) to Sustain Catch-up Growth in Previously Treated Patients with Growth Hormone Deficiency," Table 7 at 20 (1994).

39/ Letter from Wendy Arnott, Vice-President Medical, Regulatory, Quality, Linguistics, Janssen-Ortho Inc. to Health Professionals (June 26, 2002) (Volume II, Attach. 13) (stating that the scientific literature to date suggests that all exogenous proteins have the potential to elicit an immune response), available at http://www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/eprex2_e.html (last visited May 12, 2004).

Antibodies to granulocyte-macrophage colony-stimulating factor ("GM-CSF"),[40] interferon alpha ("IFNα"),[41] interferon beta ("IFNβ"),[42] interleukin 2 ("IL-2"),[43] and erythropoietin[44] have also been reported when these proteins have been produced by recombinant DNA technology and used therapeutically. For example, U.S. and European regulatory authorities were made aware of 151 cases of pure red cell aplasia ("PRCA") confirmed by bone marrow biopsy, with 112 reports of anti-erythropoietin antibodies, in patients treated with recombinant human erythropoietin (epoetin).[45] Following discussions with Health Canada, the manufacturer of Eprex (epoetin alfa), the product associated with the PCRA, issued a letter to healthcare providers reporting that in the following months to years after initiation of therapy, patients developed sudden worsening of anemia that was unresponsive to increasing doses of erythropoietin.[46] The manufacturer recommended that therapy with Eprex should be discontinued, and patients should not be switched to another erythropoietin. Reports on 13 of these patients showed all had neutralizing antibodies that could bind to epoetin and inhibit erythroid-colony formation by normal bone marrow cells, which was reversible by the addition of epoetin.[47] In all 13 patients, the antibody titer slowly decreased after discontinuation of treatment with epoetin, but the patients remained transfusion-dependent.

One report suggested that the antigenicity of the European product, Eprex, may have been enhanced by a change in the manufacturing process that altered the formulation or structure of the

---

40/ E.g., M. Wadhwa et al., 1996. Production of Neutralizing Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF) Antibodies in Carcinoma Patients Following GM-CSF Combination Therapy. Clinical and Experimental Immunology 104:351-358.

41/ E.g., R.M. McKenna and K.E. Oberg, 1997. Antibodies to Interferon-α in Treated Cancer Patients: Incidence and Significance. Journal of Interferon and Cytokine Research 17:141-143.

42/ E.g., G. Antonelli and F. Dianzani, 1999. Development of Antibodies to Interferon Beta in Patients: Technical and Biological Aspects. European Cytokine Network 10(3):413-422.

43/ E.g., A.-L. H. Skog et al., 2001. Alteration of Interleukin 2 (IL-2) Pharmacokinetics and Function by IL-2 Antibodies Induced After Treatment of Colorectal Carcinoma Patients With a Combination of Monoclonal Antibody 17-1A, Granulocyte Macrophage Colony-Stimulating Factor, and IL-2. Clinical Cancer Research 7:1163-1170.

44/ N. Casadevall et al., 2002. Pure Red Cell Aplasia and Antierythropoietin Antibodies in Patients Treated With Recombinant Erythropoietin. New England Journal of Medicine 346:469-475.

45/ Letter from Professor Alasdair Breckenridge, Chairman of Committee on Safety of Medicines (UK), to Medical Directors of NHS Trusts, Eprex (epoetin alfa) and Pure Red Cell Aplasia – Contraindication of Subcutaneous Administration to Patients with Chronic Renal Disease (Dec. 12, 2002) available at http://www.info.doh.gov.uk/doh/embroadcast.nsf/vwDiscussionAll (last visited May 12, 2004) (Volume II, Attach. 8); F-D-C- Reports, Inc., "The Pink Sheet" 64(29):11 (July 22, 2002) (Volume II, Attach. 14).

46/ Letter from Wendy Arnott, Vice-President Medical, Regulatory, Quality, Linguistics, Janssen-Ortho Inc. to Health Professionals (June 26, 2002) (Volume II, Attach. 13), available at http://www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/eprex2_e.html (last visited May 12, 2004).

47/ N. Casadevall et al., 2002. Pure Red Cell Aplasia and Antierythropoietin Antibodies in Patients Treated With Recombinant Erythropoietin. New England Journal of Medicine 346:469-475.

epoetin, because the PRCA problem has been reported in Europe much more frequently than in the United States for the same product, Procrit.[48/] However, Eprex and Procrit are manufactured by two different companies, and there have been formulation and manufacturing process changes to Eprex, including the removal of human serum albumin.[49/] As this example illustrates, the development of antibodies that neutralize biological activity, diminish clinical effectiveness, and result in serious adverse events, can be product-specific and potentially result from manufacturing and other process changes. Consequently, manufacturers of new somatropin products, such as Omnitrop™, should be required to establish the safety of their rhGH by full reports of clinical testing.

(ii) *Molecular Variants Have the Potential to Induce an Immune Response*

Immune reactions to recombinant proteins such as Omnitrop™ are thought to be a consequence of differences between native and molecular variants of the recombinant proteins that involve subtle structural changes. One type of molecular variant may involve mutations in the amino acid sequence of the recombinant protein, and it has been observed that single amino acid changes can alter the immunogenicity of rhGH. For example, rhGH that contained an additional methionine residue ("met-hGH")[50/] was shown to be equivalent to pituitary-derived hGH in animals and humans.[51/] However, an antibody response was induced in 57% (26 of 46) of children, with one child manifesting growth attenuation. In another study, 76% of 62 children with pituitary dwarfism developed antibodies to met-hGH after three months of treatment, and one child experienced growth attenuation.[52/]

Another type of molecular variant involves changes in the higher order structures of recombinant proteins (e.g., aggregates of the protein), which can generate immunogenic products with the potential for rapid densensitization, decrease in response, or other significant adverse reactions. If even a minor fraction (e.g., 1%) of a parenterally delivered protein is aggregated,

---

48/ H.F. Bunn, 2002. Drug-Induced Autoimmune Red-Cell Aplasia. New England Jounal of Medicine 346:522-523.

49/ F-D-C Reports, Inc., "The Pink Sheet" 64(29):11 (July 22, 2002) (Volume II, Attach. 14). Johnson & Johnson's Ortho Biologics division manufactures Eprex for distribution outside of the U.S., and Amgen manufactures Procrit and Epogen in the U.S.

50/ L.M. Fryklund et al., 1986. Recombinant Human Growth Hormone. Clinics in Endocrinology and Metabolism 15(3):511-535.

51/ S.L. Kaplan et al., 1986. Clinical Studies With Recombinant-DNA-Derived Methionyl Human Growth Hormone in Growth Hormone Deficient Children. Lancet 1(8483):697-700. (showing that the met-hGH was equivalent in stimulating weight gain, widening the tibial epiphysis, and raising free fatty acid concentrations in hypophysectomised rats, and in raising plasma somatomedin-C concentrations and promoting nitrogen retention in adult humans).

52/ K. Takano et al., 1986. Treatment of Pituitary Dwarfism With Methionyl Human Growth Hormone in Japan. Endocrinologicia Japonica 33(5):589-596.

adverse reactions, including anaphylactic shock, can be induced.[53/] Agitation of rhGH solutions, which can occur during lyophilization, rehydration and administration to the patient, results in aggregation.[54/] It has been demonstrated that development of antibodies to hGH during therapy is dependent on the presence of aggregated hGH in the preparation.[55/]

There is, therefore, clear potential for subtle but critical differences between differently manufactured products that may have significant differences in clinical effect, such as induction of antibodies. Accordingly, it is improper to rely on general findings of safety and public data for Genotropin® as a substitute for a direct clinical demonstration of the safety of Omnitrop™. In fact, the Omnitrop™ comparative clinical trial with Genotropin® reveals precisely such critical differences. In that trial, a high rate of anti-rhGH antibody formation occurred in children receiving Omnitrop™ (57% of patients), compared to children receiving Genotropin®.[56/] Higher concentrations of *E. coli* host cell peptides were not detected in bulk batches of Omnitrop™, necessitating the addition of two new purification steps in the Omnitrop™ process.[57/] The addition of the purification steps represents a significant change to the process and, therefore, any assumptions about the similarity of Genotropin® and Omnitrop™ derived from the earlier comparative study are no longer valid.

(iii) *Host Cell Contaminants Have the Potential to Induce an Immune Response*

FDA has stated that "[t]here are potential risks associated with host cell contaminants derived from bacteria, yeast, insect, plants, and mammalian cells. The presence of cellular host

---

53/ R.J. St. John et al., 1999. High Pressure Fosters Protein Refolding From Aggregates at High Concentrations. PNAS 96:13029-13033 (citing W.V. Moore and P. Leppert, 1980. Journal of Clinical Endocrinology and Metabolism 51:691-697; R.E. Ratner et al., 1990. Diabetes 39:728-733; C.A. Thornton and M. Ballow, 1993. Archives of Neurology 50:135-136).

54/ R.J. St. John et al., 1999. High Pressure Fosters Protein Refolding From Aggregates at High Concentrations. PNAS 96:13029-13033; N.B. Bam et al., 1998. Tween Protects Recombinant Human Growth Hormone Against Agitation-Induced Damage Via Hydrophobic Interactions. Journal of Pharmaceutical Sciences 87(12):1554-1559.

55/ W.V. Moore and P. Leppert, 1980. Role of Aggregated Human Growth Hormone (hGH) in Development of Antibodies to hGH. Journal of Clinical Endocrinology and Metabolism 51:691-697. Aggregates have also been shown to be important for immunogenicity of other therapeutic proteins. A. Braun et al., 1997. Protein Aggregates Seem to Play a Key Role Among the Parameters Influencing the Antigenicity of Interferon Alpha (IFN-α) in Normal and Transgenic Mice. Pharmaceutical Research 14(10):1472-1478.

56/ Biochemie GmbH, Study Protocol, An Open, Multicentre Phase III Study To Demonstrate The Efficacy and Safety of Omnitrop™ Lyophilised (Somatropin) in the Treatment of Growth-Deficient Children Due to Insufficient Endogenous Growth Hormone Secretion (10.02.2002), at 4 (Volume II, Attach. 4).

57/ Id.

contaminants can result in allergic reactions and other immunopathological effects."[58/] With regard to rhGH, for example, in one study, 6 of 77 children had pre-existing antibodies to periplasmic *E. coli* proteins ("PECP") and one child developed PECP antibodies after three months of rhGH therapy.[59/] Low levels of contaminating host proteins (e.g., PECP) can also act as an adjuvant and increase the immunogenicity of recombinant proteins, with development of antibodies that decrease the effectiveness of the therapeutic protein.[60/]

In addition to the presence of host cell contaminants and structural changes in the recombinant protein, a number of other factors present here, such as formulation differences, dosing, and the patient's immune status, may influence immunogenicity. Because the reasons for induction of an immune response are not well understood, however, immunogenicity can not be predicted theoretically and can only be determined directly by clinical trials.

b. There are Potential Adverse Effects Resulting From Interaction Between Molecular Variants of Omnitrop™ and Cell Proteins

There is a potential for significant adverse events if rhGH products contain aberrant forms of rhGH below the level of detection of physical and chemical tests, that can interact abnormally with other proteins in patients. GH, along with prolactin and placental lactogen, is a member of a "hormone super family" with common molecular ancestors, whose members share a number of biological, immunological, and structural characteristics.[61/] Consistent with these structural similarities and evolutionary relationships, hGH has been shown to bind not only to the growth hormone receptor, which is itself a member of a super family of receptors,[62/] but also to the receptor for human prolactin ("hPRL").[63/] Different forms of rhGH could manifest subtle differences in terms of their interaction with these different GH receptors, with a multiplicity of

---

58/ Int'l Conference on Harmonisation, Guidance for Industry: S6 Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals 2. (July 1997).

59/ J.R. Bierich, 1987. Multicentre Clinical Trial of Authentic Recombinant Somatropin in Growth Hormone Deficiency. Acta Pædiatrica Scandinavica (Supp.) 337:135-140;

60/ L.M. Fryklund et al., 1986. Recombinant Human Growth Hormone. Clinics in Endocrinology and Metabolism 15:511-535.

61/ J. Charrier and J. Martal, 1988. Growth Hormones. 1. Polymorphism. (Minireview). Reproduction, Nutrition and Development 28 (4A):857-887; J.A. Phillips III and C.L. Vnencak-Jones, 1989. Genetics of Growth Hormone and Its Disorders. Advances in Human Genetics 18:305-363.

62/ N. Billestrup et al., 1994. Identification of Intracellular Domains in the Growth Hormone Receptor Involved in Signal Transduction. Proceedings of the Society for Experimental Biology and Medicine 206(3):205-209.

63/ J.A. Wells et al., 1993. The Molecular Basis for Growth Hormone–Receptor Interactions. Recent Progress in Hormone Research 48:253-275.

unpredictable functional consequences.[64/] There is a potential for biological significance because studies have shown that differences in growth velocities in normal children with short stature may be related to the way the cellular proteins are responding to GH, rather than to the circulating concentrations of GH itself.[65/]

It has been demonstrated that mutations, such as amino acid substitutions, in GH can create variant molecules with altered binding characteristics for both the hGH and the hPRL receptors.[66/] These results are consistent with clinical observations on naturally occurring genetic mutations in the *GH1* gene.[67/] Naturally occurring mutations in the *GH1* genes of individuals with varying degrees of growth hormone deficiency have been identified,[68/] and a naturally occurring GH variant with a single amino acid substitution has been shown to bind with higher affinity to the GH receptor and inhibit the action of normal GH.[69/]

Similar variant molecules of GH protein containing mutations can be generated during the production of rhGH.[70/] During fermentation and purification processes, as well as storage of the protein, chemical modifications have been reported to occur in hGH.[71/] For example, during production of rhGH in *E. coli*, a variant is generated with a trisulfide bond at Cys182-Cys189 in

---

64/ E.g., M.D. Lewis et al., 2004. A Novel Dysfunctional Growth Hormone Variant (Ile179Met) Exhibits a Decreased Ability to Activate the Extracellular Signal-regulated Kinase Pathway. Journal of Clinical Endocrinology & Metabolism 89:1068-1075.

65/ D.E. Codner et al., 2000. Relationship Between Serum Growth Hormone Binding Protein Levels and Height in Young Men. Journal of Pediatric Endocrinology & Metabolism 13:887-892.

66/ J.A. Wells et al., 1993. The Molecular Basis for Growth Hormone–Receptor Interactions. Recent Progress in Hormone Research 48:253-275.

67/ E.g., J.D. Cogan and J.A. Phillips, III, 1998. Growth Disorders Caused by Genetic Defects in the Growth Hormone Pathway. Advances in Pediatrics 45:337-361; A.M. Procter et al., 1998. The Molecular Genetics of Growth Hormone Deficiency. Human Genetics. 103:255-272.

68/ E.g., H. Abdul-Latif et al., 2000. Growth Hormone Deficiency Type IB Caused by Cryptic Splicing of the GH-1 Gene. Journal of Pediatric Endocrinology & Metabolism 13:21-28; Y. Hasegawa et al., 2000. Identification of Novel Human GH-1 Gene Polymorphisms That Are Associated with Growth Hormone Secretion and Height. Journal of Clinical Endocrinology & Metabolism 83:1290-1295; D.S. Millar et al., 2003. Novel Mutations of the Growth Hormone 1 (GH1) Gene Disclosed by Modulation of the Clinical Selection Criteria for Individuals With Short Stature. Human Mutation 21:424-440; M. Horan et al., 2003. Human Growth Hormone 1 (GH1) Gene Expression: Complex Haplotype-dependent Influence of Polymorphic Variation in the Proximal Promoter and Locus Control Region. Human Mutation 21:408-423.

69/ A.M. Procter et al., 1998. The Molecular Genetics of Growth Hormone Deficiency. Human Genetics. 103:255-272.

70/ G. Karlsson et al., 1999. Separation of Oxidized and Deaminated Human Growth Hormone Variants by Isocratic Reversed-Phase High-Performance Liquid Chromatography. Journal of Chromatography 855:147-155.

71/ E.C. Roswall et al., 1996. Novel Assays on Human Growth Hormone Receptor as Alternatives to the Rat Weight Gain Bioassay for Recombinant Human Growth Hormone. Biologicals 24:25-39.

addition to the native disulfide form.[72] These variants that are formed during industrial scale production of rhGH, and that may be present at levels below the level of detection of physical and chemical tests, could interact abnormally with other proteins in the body to disrupt normal metabolic functions. It is, therefore, necessary to demonstrate the safety of rhGH products, such as Omnitrop™, through clinical trials conducted in a sufficiently large population of test subjects to capture the full range of genetic polymorphism of potential GH receptors.

c. Low Levels of Contaminating Proteins Can Directly Result in Adverse Events

FDA's stated preference is to rely "on purification processes to remove impurities and contaminants,"[73] rather than relying on identification and quantitation of impurities and contaminants for rDNA products. As a result, FDA-approved rDNA products may contain uncharacterized impurities and/or contaminants at low levels. In turn, the only way an applicant can demonstrate that its product does not contain uncharacterized impurities and/or contaminants that could result in potentially significant adverse effects is to conduct clinical safety and effectiveness trials.

Some host cell components, such as bacterial endotoxin, have been shown to cause adverse events, such as fever in the case of endotoxin.[74] Humans are the most sensitive animal studied for response to *E. coli* endotoxin, with a minimal pyrogenic dose of 0.1 – 0.5 ng/kg.[75] Other bacterial components are able either to trigger inflammatory pathways directly, or to stimulate target cells (such as monocytic cells, peripheral mononuclear cells or endothelial cells).[76] The ability of small quantities of microbial proteins to induce proinflammatory cytokines is well known.[77] It is also

---

[72] M. K. Thomsen et al., 1994. Pharmacological Characterization of a Biosynthetic Trisulfide-Containing Hydrophobic Derivative of Human Growth Hormone: Comparison with Standard 22 K Growth Hormone. Pharmacology & Toxicology. 74:351-358; E. Canova-Davis et al., 1996. Confirmation by Mass Spectrometry of a Trisulfide Variant in Methionyl Human Growth Hormone Biosynthesized in Escherichia coli. Analytical Chemistry. 68:4044-4051; C. Andersson et al., 1996. Isolation and Characterization of a Trisulfide Variant of Recombinant Human Growth Hormone Formed During Expression in Escherichia coli. International Journal of Peptide & Protein Research. 47:311-321; E. Strandberg et al., 1997. Nuclear Magnetic Resonance Studies of the C-terminal Human Growth Hormone Fragment I179-C182-[SS]-C189-P191 and the Related Trisulfide Peptide I179-C182-[SSS]-C189-P191. Journal of Peptide Research. 49:254-260.

[73] Int'l Conference on Harmonisation, Guidance for Industry: S6 Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals 2. (July 1997).

[74] E.T. Rietschel et al., 1994. Bacterial Endotoxin: Molecular Relationships of Structure to Activity and Function. FASEB Journal 8:217-225.

[75] C.A. Dinarello, 1983. Molecular Mechanisms in Endotoxin Fever. Agents and Actions 13:470-486.

[76] G. Zanetti et al., 1997. Sepsis and Septic Shock. Swiss Medical Weekly 127(2):489-499.

[77] B. Henderson et al., 1996. Bacterial Modulins: A Novel Class of Virulence Factors Which Cause Host Tissue Pathology by Inducing Cytokine Synthesis. Microbiological Reviews 60:316-341.

now recognized that bacteria produce many molecules that have profound effects on the capacity of cells in humans to produce selected cytokine networks, which constitute an important part of the innate immune response.[78/]

Given this risk of adverse events from contaminants that could be present in new rDNA products at levels below detection of physical and chemical assays, it is necessary to assess the safety of Omnitrop™ through extensive clinical studies.

6. Follow-on Versions of Genotropin® Must be Supported by Clinical Trials That Specifically Address Efficacy

a. Mutations Below the Level of Detection Have the Potential to Cause Reduced Efficacy

Changes in amino acid sequence due to low levels of mutation in the recombinant plasmid (i.e., nucleotide substitutions in the plasmid), or errors in translation (e.g., norleucine incorporation[79/]) that are below the level of detection and thus not identified in the CMC documentation, can reduce the effectiveness of recombinant protein products. Because these mutations are present at a low level, *in vitro* bioassays are unlikely to be sufficiently sensitive to detect abnormal activity in rhGH products, and the mutated proteins could easily remain undetected in comparability assays. But when products with such mutations are repeatedly injected at higher doses in humans, there is the potential for reduced effectiveness. Extensive clinical testing is, therefore, necessary to ensure the quality and efficacy of new rDNA products.

b. Changes in the Structures of Recombinant Proteins Such as Omnitrop™ Can Reduce Efficacy

Omnitrop™ is a soluble protein that folds into its normal tertiary structure in solution.[80/] But proteins such as Omnitrop™ undergo chemical decomposition if stored in solution.[81/] To reduce chemical degradation during storage, Omnitrop™ and other recombinant proteins are lyophilized or freeze-dried. Lyophilization, however, may cause the formation of aggregates or irreversible denaturation of the protein, which can result in a loss of biological activity.[82/]

78/ M. Wilson et al., 1998. Bacterial Perturbation of Cytokine Networks. Infection and Immunity 66:2401-2409.

79/ G. Bogosian et al., 1989. Biosynthesis and Incorporation into Protein of Norleucine by Eschericia coli. Journal of Biological Chemistry 264:531-539.

80/ D.N. Brems et al., 1990. Equilibrium Denaturation of Human Growth Hormone and Its Cysteine-Modified Forms. Journal of Biological Chemistry 265:5504-5511; K.M. Youngman et al., 1995. Kinetic Analysis of the Folding of Human Growth Hormone. Influence of Disulfide Bonds. Journal of Biological Chemistry 270:19816-19822.

81/ M.J. Pikal et al., 1991. The Effects of Formulation Variables on the Stability of Freeze-Dried Human Growth Hormone. Pharmaceutical Research 8(4):427-436.

82/ Id.

Although methods exist for the analysis of structural changes to the protein,[83] these methods are limited in their ability to detect subtle changes that may inactivate proteins. For example, it has recently been shown that a therapeutic antibody lost substantial biological activity after lyophilization, despite the absence of significant differences in many analytical tests.[84] It has also been shown that excipients can induce aggregation with considerable loss in biological activity.[85]

Thus, determining the correct structure, or correct folding of a recombinant protein, to ensure adequate biological activity is technically challenging. In the case of hGH, incorrect folding of the protein has been proposed as the mechanism that is responsible for dominant-negative protein mutants that are not only inactive, but can also inactivate correctly folded proteins, and cause hormone deficiency.[86] Consequently, it is necessary that Sandoz conduct clinical trials to ensure that the proteins in Omnitrop™ have the correct molecular and folding structure.

c. Bioassays for Growth Hormone Activity Are Not Adequate to Predict Clinical Efficacy of Omnitrop™

It is well recognized that bioassays do not predict clinical efficacy.[87] Rather, bioassays are used by regulatory authorities to ensure product potency, stability, and batch-to-batch consistency, only after establishing a correlation between activity in bioassays and the expected response in clinical trials.[88] Moreover, bioassays are often criticized as being variable and non-specific, and standard cGMP practices are to select a reproducible bioassay, irrespective of its clinical relevance, to ensure reliability.[89] For example, in discussing potency assays, ICH guidance states that: "[m]imicking the biological activity in the clinical situation is not always necessary. A correlation

---

83/ E.g., B. DiPaolo et al., 1999. Monitoring Impurities in Biopharmaceuticals Produced by Recombinant Technology. Pharmaceutical Science and Technology Today 2(2):70-82.

84/ N. Taschner et al., 2001. Modulation of Antigenicity Related to Changes in Antibody Flexibility upon Lyophilization. Journal of Molecular Biology 310:169-179.

85/ L. Runkel et al., 1998. Structural and Functional Differences Between Glycosylated and Non-Glycosylated Forms of Human Interferon-β (IFN-β). Pharmaceutical Research 15:641-649.

86/ P.S. Dannies, 2000. Protein Folding and Deficiencies Caused by Dominant-Negative Mutants of Hormones. Vitamins and Hormones 58:1-26; M.S. Lee et al., 2000. Autosomal Dominant Growth Hormone (GH) Deficiency Type II: The Del32-71-GH Deletion Mutant Suppresses Secretion of Wild-type GH. Endocrinology 141:883-890.

87/ R. Thorpe et al., 1997. The Use of Bioassays for the Characterisation and Control of Biological Therapeutic Products Produced by Biotechnology. In: Development of Specifications for Biotechnology Pharmaceutical Products. F. Brown and J. Fernandez (Eds.) 91:79-88 (stating that "clinical efficacy and safety must obviously be directly assessed in clinical trials in humans").

88/ Id.

89/ Id.

between the expected clinical response and the activity in the biological assay should be established in pharmacodynamic or clinical studies."[90/]

Clinical trials are also necessary to ensure the effectiveness of rhGH because the available assays for measuring biological activity of GH preparations have significant theoretical and practical limitations. There are many effects of hGH, including metabolic effects (e.g., stimulation of protein synthesis and lipolysis, and inhibition of insulin action on glucose metabolism), physiological effects (e.g., stimulation of new bone formation and erythropoiesis), and anatomical effects (e.g., acceleration of linear growth, reduction of adipose mass, and increase in lean body mass),[91/] and, consequently, no single assay except clinical testing provides an appropriate measure of activity. Moreover, the demonstration of purity and identity of rhGH is insufficient to establish biological activity, because not all of the chemical and physical aspects contributing to bioactivity are known.[92/]

For example, two of the *in vivo* assays used to measure growth-promoting activity involve monitoring weight gain in rats receiving daily injections of hGH, and measuring growth of a segment of the tibia of young rats receiving daily injections of hGH.[93/] These *in vivo* assays have been criticized as being "insensitive . . . [and] imprecise,"[94/] and have a limitation of testing activity of a human protein in a heterologous species. This weakness or limitation is evidenced by testing of bovine growth hormone, which is not active in humans, and which is only 66% identical in amino acid sequence to human growth hormone, but which is nearly equivalent to human growth hormone in the rat weight gain bioassay.[95/]

90/ Int'l Conference on Harmonisation, Guidance on Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products, 64 Fed. Reg. 44928, 44930 (Aug. 18, 1999).

91/ R.K. Chawla et al., 1983. Structural Variants of Human Growth Hormone: Biochemical, Genetic, and Clinical Aspects. Annual Review of Medicine 34:519-547.

92/ E.C. Roswall et al., 1996. Novel Assays Based on Human Growth Hormone Receptor as Alternatives to the Rat Weight Gain Bioassay for Recombinant Human Growth Hormone. Biologicals 24(1):25-39.

93/ A.F. Bristow and S.L. Jeffcoate, 1991. Assay of rDNA Growth Hormone. Pharmeuropa 3:3-20; A.F. Bristow and S.L. Jeffcoate, 1992. Analysis of Therapeutic RhGH Preparations: Report of an Interlaboratory Collaborative Study on RhGH Assay Methodologies. Biologicals 20:221-231.

94/ M.T. Dattani, 1999. Measurement of Growth Hormone. In: Growth Hormone Therapy in KIGS, 10 Years Experience. M.B. Ranke and P. Wilton (Eds.) Johann Ambrosius Barth Verlag (Heidelberg) 43-51.

95/ E.C. Roswall et al., 1996. Novel Assays Based on Human Growth Hormone Receptor as Alternatives to the Rat Weight Gain Bioassay for Recombinant Human Growth Hormone. Biologicals 24(1):25-39 (citing M.D. Grosbeck and A.F. Parlow, 1987. Highly Improved Precision of the Hypophysectomized Female Rat Body Weight Gain Bioassay for Growth Hormone by Increased Frequency of Injections, Avoidance of Antibody Formation, and Other Simple Modifications. Endocrinology 120:2582-2590).

Additional evidence of the imprecision of the *in vivo* bioassays for rhGH is found in the statistical limits originally specified in the European Pharmacopoeia.[96/] The specified statistical limits of the estimate of biological activity are 80 to 125%, with fiducial limits (95% confidence intervals) of 64 to 156%. This wide range reflects the statistical imprecision of the assay.

Because the bioassays have limited sensitivity, more sensitive assays (e.g., binding to cultured human lymphocytes or rodent hepatocytes) and radioimmunoassays that use antibodies to detect GH, have been developed.[97/] Although more sensitive, these assays are also limited because binding to receptors is only the first step in the GH mechanism of action,[98/] and radioimmunoassays detect "GH-like" molecules because antibodies only recognize parts of GH.[99/] Thus, these bioassays do not provide the scope or specificity of evidence necessary to determine efficacy.

The variability and lack of precision in these assays were convincingly demonstrated in a collaborative study among a number of pharmaceutical industry and national control laboratories that were asked to assay a set of growth hormone preparations, some of which had been degraded or modified.[100/] For the *in vivo* bioassays, generally considered to be the "gold standard" assays because they measure growth, individual laboratories estimated the potency of a sample with an assigned potency of 17.2 U/vial as ranging from 10.6 to 27.9 U/vial. For a sample that had undergone extensive protein degradation, not one laboratory found the sample to be inactive, and in fact three laboratories did not distinguish the degraded sample from the intact sample. For the *in vitro* assays, estimates of the 17.2 U/vial sample ranged from 29.3 to 39.6 U/vial, and estimates using receptor assays ranged from 14.28 to 24.8 U/vial. Immunoassays "generally appeared to be the least discriminating technique used in the study."[101/]

These results demonstrate the significant limitations of bioassays to establish the identity, purity, and potency of hGH. More specifically, the results show that: (1) identity can not be established because the degraded sample contained no native or non-degraded hGH, as assayed by

---

96/ European Pharmacopoeia 556 (Council of Europe 2d ed.) (1987).

97/ R.K. Chawla et al., 1983. Structural Variants of Human Growth Hormone: Biochemical, Genetic, and Clinical Aspects. Annual Review of Medicine 34:519-547. It has also been pointed out that not all laboratories use the same primary reference standard, which can result in discrepant results between laboratories. A.F. Bristow, 1999. International Standards for Growth Hormone. Hormone Research 51(suppl 1):7-12.

98/ A.L. Rosenbloom et al., 1997. Growth Hormone Insensitivity. Pediatric Endocrinology 44(2):423-442.

99/ C.J. Strasburger and M.T. Dattani, 1997. New Growth Hormone Assays: Potential Benefits. Acta Pædiatrica (Supp.) 423:5-11.

100/ A.F. Bristow and S.L. Jeffcoate, 1992. Analysis of Therapeutic Growth Hormone Preparations: Report of an Interlaboratory Collaborative Study on Growth Hormone Assay Methodologies. Biologicals 20:221-231; A.F. Bristow and S.L. Jeffcoate, 1991. Assay of rDNA Growth Hormone. Pharmeuropa 3:3-20 (participating in the study were 10 laboratories, including 1 from FDA).

101/ Id.

physical methods, but this was not able to be identified by some laboratories; (2) purity can not be established because the relative insensitivity of the bioassays to profound degradation suggests that impurities would not have been detected; and (3) there is a limitation in establishing potency, based on the wide ranges in activity identified by the assays.

There is, therefore, general recognition that available bioassays for measuring rhGH activity are insensitive and imprecise, may have little relevance to clinical activity, and are not designed for use by regulatory authorities to predict clinical efficacy. As a result, Sandoz must conduct full clinical trials to ensure the effectiveness of Omnitrop™.

7. Because Genotropin® and Omnitrop™ Have Different Active Ingredients and Formulations, Omnitrop™ Cannot be Approved in Reliance on Pfizer's Proprietary Clinical and CMC Information for Genotropin®

The significant chemical and formulation differences between Omnitrop™ and Genotropin® scientifically preclude reliance on the Genotropin® clinical and CMC information to support the approval of Omnitrop™.

a. There are Significant Compositional and Manufacturing Differences Between Omnitrop™ and Genotropin®

(i) *The Products Have Significantly Different Molecular Weights*

As noted above, the molecular weight of the somatropin in Genotropin® is 22,124 daltons, compared to 21,125 daltons for Omnitrop™. Molecular weight is a critical defining characteristic of a biological molecule, and FDA has previously viewed molecular weight as a key distinguishing characteristic for biotherapeutic products.[102/] It should do so here.

For example, FDA's actions and statements related to its consideration of a follow-on iron dextran product, underscores the importance the Agency places on molecular weight distribution. Iron dextran is a complex of ferric hydroxide and low molecular weight dextrans indicated for treatment of iron deficient patients in whom oral administration is unsatisfactory or impossible. On August 30, 1991, Luitpold submitted an abbreviated new drug application ("ANDA") for its iron dextran product Dexferrum®. Throughout the Dexferrum® approval process, FDA expressed concerns regarding the safety and effectiveness of the purportedly-similar follow-on iron dextran—specifically, that the complex composition of iron dextran, the molecular weight differences between the innovator and follow-on formulations, and the possibility of physicochemical differences introduced by proprietary manufacturing methods, require that follow-on iron dextran formulations be tested for safety and effectiveness in clinical trials.

[102/] See, e.g., Int'l Conference on Harmonisation, Guidance for Industry, Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products (Aug. 1999) (citing molecular weight or size as a principal feature to evaluate the physicochemical properties of a biotechnological or biological product).

FDA refused Luitpold's initial request for an in vivo bioequivalence waiver, in part, because of "the dramatic difference in molecular weight between the test product and reference drug,"[103] and refused a second waiver request because "in view of the background of tremendous variability in effective bioavailability for IV administered iron dextran it might be impossible to demonstrate in-vivo differences between the products...."[104] Further waiver requests by Luitpold were also denied. Notably, FDA commented that, "[a]side from molecular weight differences there might be other physicochemical differences resulting from probably different methods of production ... which might matter in terms of efficacy."[105]

Consistent with the foregoing, because the active pharmaceutical ingredients in Genotropin® and Omnitrop™ are different, the CMC documentation and clinical data establishing the safety and effectiveness of Genotropin® properly can not be relied upon, referenced, or used to approve a marketing application for Omnitrop™.

(ii) *The Products Likely Have a Different Genetic Sequence of Their Recombinant Plasmids*

A significant difference in the manufacturing process between Genotropin® and Omnitrop™ is the independent derivation of the recombinant plasmid that encodes the primary amino acid sequence of the GH. The sequence of the recombinant plasmid used to manufacture Genotropin® is proprietary information, and it can not be compared to the recombinant plasmid used to manufacture Omnitrop™. FDA requires detailed descriptions, including complete nucleotide sequence, of the gene and expression vector system for recombinant DNA products.[106] Because there may be differences between these two recombinant plasmids, it is improper to rely on, reference, or use the CMC documentation and clinical testing for Genotropin® to approve a marketing application for Omnitrop™.

(iii) *The Products Have Different Master and Working Cell Banks*

Another significant difference in the manufacturing process between Genotropin® and Omnitrop™ is the independent derivation for each product of master cell banks and working cell banks, which are established from the master cell banks. The introduction of new master and working cell banks has the potential to generate different impurity profiles, contaminants, and

---

103/ Luitpold Dexferrum® Summary Basis of Approval. Review of a Second Request for Waiver of Bioequivalence Study on an Injectable Dosage Form (Oct. 5, 1992). Reviewer James E. Chaney.

104/ Id.

105/ Luitpold Dexferrum® Summary Basis of Approval. Review of an Amendment in Support of Pharmaceutical Equivalence and Two Waiver Requests (Mar. 22, 1993). Reviewer James E. Chaney.

106/ Food and Drug Admin., Guidance for Industry, For the Submission of Chemistry, Manufacturing, and Controls Information for a Therapeutic Recombinant DNA-Derived Product or a Monoclonal Antibody Product for In Vivo Use (Aug. 1996).

molecular variants.[107] For example, the draft U.S. Pharmacopoeia monograph for Somatropin states that the presence of host cell DNA and host cell protein impurities in somatropin are process-specific.[108] Sandoz does not have access to Pfizer's proprietary information on product characterization to ascertain the impact of variations in the master and working cell banks on the safety and effectiveness of Omnitrop™.

(iv) *The Products Have Different Formulations: Lack of Mannitol in Lyophilized Powder and Addition of Preservative Benzyl Alcohol*

Differences in the formulation of Genotropin® and Omnitrop™ preclude reliance on or use of the clinical and CMC information that establishes the safety and effectiveness of Genotropin®. In the drug powder of Genotropin®, there is 1.8 mg mannitol, which is not present in the drug powder of Omnitrop™. There are also significant differences in the formulation of the diluents for the two products. Genotropin® contains mannitol and m-cresol in the diluent, whereas Omnitrop™ contains benzyl alcohol, but not mannitol or m-cresol.

Pfizer has proprietary data demonstrating the importance of mannitol in maintaining the stability of the rhGH in Genotropin®. These differences in formulation, that are described in Sandoz' notice of patent certification to Pfizer, have the potential to increase changes in the higher order structures of recombinant proteins, including aggregates, that can generate immunogenic products and cause significant adverse reactions.

Sandoz has positioned Omnitrop™ as a new liquid formulation,[109] and because of these significant differences in formulation, the safety and effectiveness of Omnitrop™ must be independently demonstrated, without reliance on or use of the clinical or CMC information for Genotropin®.

(v) *The Products Use Drastically Different Containers*

The use of different containers for Genotropin® and Omnitrop™, as described in the Sandoz' notice of patent certification to Pfizer, can result in significant differences in the stability of the two products. Pfizer has proprietary data demonstrating the impact of container materials on the stability of its rhGH. Sandoz, therefore, must independently demonstrate the quality of Omnitrop™ in its container system, without reliance on Pfizer's proprietary information.

107/ Int'l Conference on Harmonisation, Q5D Quality of Biotechnological/Biological Products: Derivation and Characterization of Cell Substrates Used for Production of Biotechnological/Biological Products (Sept. 1998).

108/ The U.S. Pharmacopoeial Convention Inc., 1998. Somatropin In-Process Revision, Pharmacopoeial Forum 25(4):6866-6875.

109/ F. Peter et al. Long-Term (21 Months) Efficacy and Safety of New Liquid Recombinant Human Growth Hormone (Omnitrop™ Solution for Injection) in Pretreated Short Children with Growth Hormone Deficiency. (The year and publication of this abstract are unknown).

(vi) *The Products Have Different Reconstitution Procedures*

Different reconstitution procedures for Genotropin® and Omnitrop™ have the potential to affect the quality of the rhGH drug product. Pfizer has developed two semi-automatic reconstitution processes. In one process using Pfizer's Genotropin® Pen, Genotropin® is dispensed in a two-chamber cartridge, with lyophilized somatropin in the front chamber and diluent in the rear chamber, which provides for reconstitution by controlled fluid flow. This results in a controlled reconstitution speed that maintains the quality of the therapeutic protein. In the second process, reconstitution is similarly controlled through use of the Genotropin Mixer® to avoid development of particulate matter or discoloration.

In contrast, Sandoz' notice of patent certification states that Omnitrop™ will be dispensed in a vial containing the lyophilized somatropin, and a second, separate vial will be provided that contains the diluent. Reconstitution of Omnitrop™ is a manual procedure with a syringe and needle, which results in an uncontrolled process. An uncontrolled process has the potential to increase aggregation of the protein, which can generate immunogenic products and cause significant adverse reactions. Consequently, FDA can not rely on or use the demonstrated quality, safety, and effectiveness of Genotropin® to support the marketing application of Omnitrop™.

(vii) *The Products Have Differences in Delivery Systems and Dosing*

Differences in the delivery systems for Genotropin® and Omnitrop™ likely result in administration of different doses of rhGH. Genotropin® is delivered by a closed system injection pen, which provides a more controlled dose. In contrast, the dose of Omnitrop™ is determined by manual transfer of diluent from one vial to a second vial containing the somatropin during reconstitution using a syringe and needle, which results in variability, through evaporation and handling, in the administered dose of rhGH. The results of clinical testing and marketing experience with Genotropin®, therefore, can not be used to support the marketing application of Omnitrop™. Furthermore, Sandoz' notice of patent certification does not specify the device for subcutaneous injection. FDA must ensure that there is sufficient independent testing to establish the safety and effectiveness of the Omnitrop delivery system and dosing.

b. Existing Information for Omnitrop™ is Inadequate to Scientifically Support Reliance on the Genotropin® Clinical Data and Manufacturing Process, Methods, and Specifications

There are substantial product and manufacturing differences between Omnitrop™ and Genotropin® and, as documented above, there is inadequate information upon which to scientifically evaluate these differences. The critical information necessary to determine the similarity of the Genotropin® and Omnitrop™ product characteristics and processes is proprietary Pfizer data, some of which is not included in the NDA for Genotropin®. Consequently, because Genotropin® and Omnitrop™ have different active ingredients and formulations, and these differences cannot be scientifically evaluated, Omnitrop™ properly cannot be approved in reliance on the clinical/CMC information establishing the safety and effectiveness of Genotropin®.

8. The Public Omnitrop™ Data are Insufficient Alone to Support its Approval

Because of the recognized potential for significant adverse events associated with rhGH products due to the generation of antibodies, interaction between aberrant growth hormone and other proteins in patients, low levels of contaminating proteins, mutations below the level of detection, and changes in structure, such as aggregates, FDA has required extensive clinical testing to establish the safety and effectiveness of new rhGH products.

FDA has considered each of the eight approved innovator rhGH drug products—Genotropin®, Nutropin®, Protropin®, Humatrope®, Norditropin®, Tev-tropin®, Saizen®, and Zorbtive™—to be unique, and has required full indication-specific clinical trials, pre-clinical data, and CMC information to establish their safety and effectiveness. The Agency has consistently upheld these rigorous standards for rhGHs and based its product approvals on firm scientific principles. The publicly available Omnitrop™ data are inadequate to independently establish Omnitrop™'s safety or effectiveness, or to account for the formulation, manufacturing, and packaging differences between Omnitrop™ and Genotropin®. If FDA approves the Omnitrop™ section 505(b)(2) application, FDA will improperly and unjustifiably be lowering its rigorous approval standards that historically have served patients well for these products.

a. The Public Omnitrop™ Studies Reveal Only Limited Clinical Testing

The publicly available data reveal only limited and inadequate clinical testing of Omnitrop™, and these studies have noteworthy methodological shortcomings. Two efficacy studies with Omnitrop™ have been limited to testing in children with GHD,[110/] and the studies are poorly designed. As noted above, in addition to children with GHD, Genotropin® is indicated for adults with GHD, children with Prader-Willi Syndrome, and children born small for gestational age who fail to manifest catch-up growth. None of Sandoz' studies address these important populations for rhGH therapy.

110/ References to two additional study protocols were identified, but no further information about the studies was found to indicate that the studies had been conducted. One was a Biochemie GmbH study protocol entitled "An Open, Multicenter Phase III Study to Demonstrate the Efficacy and Safety of Omnitrop™ Lyophilised (Somatropin) in the Treatment of Growth-Deficient Children Due to Insufficient Endogenous Growth Hormone Secretion" (Clinical Trial ID-No.: EP2K-02-PhIII-Lyo) (Volume II, Attach. 4). The second study was identified in an Internet listing of current (in 2002) research interests of the staff of the pediatric service at the Ramon y Cajal Hospital in Madrid, Spain (Yturriaga R., Open, Multicentre, Phase III Study of a Liquid Formulation of Growth Hormone (Omnitrop™) for Growth Hormone Deficiency (GHD) in Children and Girls with Turner Syndrome. Biochemie GMBH. Protocol EP2K-00PhIIIb-E). See Hospital Ramón y Cojal, Actividad de Investigación y Docencia, available at http://www.hrc.es/info/memoria2002/pediatria.htm (last visited May 12, 2004) (Volume II, Attach. 15).

The initial Omnitrop™ efficacy study was an unblinded clinical trial comparing daily administration of Omnitrop™ and Genotropin® for nine months,[111] and the second Omnitrop™ efficacy study was unblinded and uncontrolled in GHD children who had previously received Genotropin® for nine months.[112] FDA has emphasized that the most important design techniques for avoiding bias in clinical trials are blinding and randomization to an adequate control group, to prevent study subjects and investigators from unconsciously and/or consciously influencing the results of a study.[113] Indeed, FDA expects blinding and randomization to be normal features of clinical trials included in a marketing application.[114] An appropriate control group, such as comparison to another active drug, "is important to minimize the likelihood of erroneous inference."[115] By failing to incorporate these fundamental methodological features, the results of the Sandoz studies must be viewed with corresponding skepticism.

A third comparative crossover study comparing Omnitrop™ and Genotropin® in 24 healthy subjects was designed to examine pharmacokinetic and pharmacodynamic properties, and only followed subjects for adverse events for two weeks.[116] The relatively limited two-week safety data provided by this study presents appreciable concerns given the many known adverse events for rhGH identified over the long course of therapy, and because the only other safety information apparently was provided indirectly through the efficacy studies described above.

Consistent with the foregoing, the publicly available data reveal that the clinical testing for Omnitrop™ is limited in scope and duration, and raises many unanswered questions about the safety and efficacy of this product.

b. The Public Omnitrop™ Data are Inadequate to Establish its Safety and Effectiveness

In contrast to the incremental product changes implemented and validated by Pfizer over many years with respect to the well-established and validated Genotropin® manufacturing process,

---

111/ T. Romer et al. Efficacy of a Recombinant Human Growth Hormone (Omnitrop™) in a Randomised, Comparative Clinical Trial in Children with Growth Failure Due to Growth Hormone Deficiency. (The year and publication of this abstract are unknown.)

112/ F. Peter et al. Long-Term (21 Months) Efficacy and Safety of New Liquid Recombinant Human Growth Hormone (Omnitrop™ Solution for Injection) in Pretreated Short Children with Growth Hormone Deficiency. (The year and publication of this abstract are unknown.)

113/ Int'l Conference on Harmonisation, Guidance on General Considerations for Clinical Trials, 62 Fed. Reg. 66,113, 66,118. (Dec. 17, 1997); Int'l Conference on Harmonisation, Guidance for Industry: E9 Statistical Principles for Clinical Trials 10. (Sept. 1998).

114/ Id.

115/ 62 Fed. Reg. 66,117.

116/ This Phase I study is discussed in the Biochemie GmbH, Study Protocol, "An Open, Multicenter Phase III Study to Demonstrate the Efficacy and Safety of Omnitrop™ Lyophilised (Somatropin) in the Treatment of Growth-Deficient Children Due to Insufficient Endogenous Growth Hormone Secretion" (Clinical Trial ID-No.: EP2K-02-PhIII-Lyo) (Volume II, Attach. 4).

Sandoz has established a wholly new manufacturing process without the benefit of such historical data and expertise. As might be expected, Sandoz has experienced significant process problems that have clinical consequences.

Specifically, Sandoz' October 2002 Phase III study protocol[117/] explains that, due to higher concentrations of *E. coli* host cell peptides ("ECP") that were masked in the Omnitrop™ bulk batch, a higher rate of antibody formation was found in the Omnitrop™ group of GHD children, compared to the Genotropin® group (57% vs. 2%).[118/] While Sandoz asserts in this same protocol that the ECP was removed by new purification steps to produce subsequent Omnitrop™ batches, the fact that Omnitrop™ has been shown to be more antigenic than Genotropin® raises threshold concerns about the Sandoz process, and is indicative of the risks associated with a de novo rhGH manufacturing process. In Sandoz' other clinical trial, 4.5% of the children (2/44) developed anti-GH antibodies.[119/] While the abstract for this study states that the "prevalence of [antibodies is] comparable to that reported for other hGH preparations," the study results demonstrate a higher level of antibodies for Omnitrop™ than approved rhGH formulations such as Genotropin®. It remains to be seen whether the sufficiency of Sandoz' additional purification steps can be demonstrated empirically in a clinical setting, and whether these or other process changes produce additional problems with clinical consequences, which may be magnified when Sandoz expands manufacturing to commercial scale batches. Without the benefit of historical process information or adequate clinical trials such as that possessed by Pfizer, Sandoz' Omnitrop™ manufacturing process likely may continue to produce unpredictable results. Comparative trials conducted with Omnitrop™ and Genotropin® prior to changes in the manufacturing process for Omnitrop™ cannot support the safety of the pending application because the changes introduced to the manufacturing method can induce changes in stability and structure of the rhGH molecule.

Moreover, while Sandoz is asserting that Omnitrop™ has a similar effectiveness profile to that of Genotropin®, it apparently has only conducted one study comparing Genotropin® and the product for which Sandoz is seeking approval.[120/] This level of evidence is inadequate under FDA's requirement for two controlled clinical studies.[121/]

117/ Biochemie GmbH, Study Protocol, An Open, Multicentre Phase III Study To Demonstrate The Efficacy and Safety of Omnitrop™ Lyophilised (Somatropin) in the Treatment of Growth-Deficient Children Due to Insufficient Endogenous Growth Hormone Secretion (10.02.2002) (Volume II, Attach. 4).

118/ Id. at 4.

119/ F. Peter et al. Long-Term (21 Months) Efficacy and Safety of New Liquid Recombinant Human Growth Hormone (Omnitrop™ Solution for Injection) in Pretreated Short Children with Growth Hormone Deficiency. (The year and publication of this abstract are unknown).

120/ T. Romer et al. Efficacy of a Recombinant Human Growth Hormone (Omnitrop™) in a Randomised, Comparative Clinical Trial in Children with Growth Failure Due to Growth Hormone Deficiency. (The year and publication of this abstract are unknown).

121/ Food and Drug Admin., Guidance for Industry, Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products (May 1998) (stating that is has been FDA's position that the

(Continued)

The public information about Omnitrop™ also indicates that Sandoz has not conducted Phase II dosing studies, even though, as explained above, differences in the delivery systems for Genotropin® and Omnitrop™ likely result in administration of different doses of rhGH of each product. Accordingly, the Genotropin® dose and dosing schedule information, including the clinical testing and experience with the Genotropin® injection pen, are irrelevant to Omnitrop™, and Sandoz must conduct appropriate independent Phase II dosing studies for its product.

Additionally, it does not appear that Sandoz has conducted adequate pre-clinical studies of Omnitrop™. Sandoz reportedly has analyzed the active component of Omnitrop™ using physico-chemical, immunological, chromatographic and electrophoretic testing, and conducted a study in rats to assess the toxic effects of clinical significance to humans up to doses of 8 mg/kg/day for a period of 14 days. While Sandoz has conducted these analyses of Omnitrop™, it apparently has failed to conduct suitable pharmacological and toxicological testing in animals and cell lines. The one reported pre-clinical study in rats appears to be a 14-day mini-toxicology study in rats—an inappropriate species because rats develop antibodies to human growth hormone in ten days, and GH exerts a lactogenic effect in rats, which can complicate the interpretation of the test results. In contrast, three month monkey repeat dose toxicity studies were submitted as part of the initial filing of Genotropin® in 1987, and a 12 month monkey study was subsequently submitted. Therefore, additional pre-clinical data is necessary to ensure the safety of Omnitrop™ for chronic use in children and adults for physiological replacement therapy.

9. Sandoz' Product Cannot be "A" Rated

FDA determines drug products to be therapeutically equivalent only if, among other showings, the products are pharmaceutically- and bio-equivalent.[122/] For both legal and scientific reasons, Omnitrop™ does not meet these requirements, and, therefore, can not be determined to be therapeutically equivalent to Genotropin®.

Pfizer has previously asserted that FDA may only assign "A" therapeutic equivalence evaluation codes to drug products approved under section 505(j) of the FFDCA.[123/] In its October 14, 2003 response to the three citizen petitions concerning section 505(b)(2) applications, FDA granted "certain specific portions of the petitions ... related to the therapeutic equivalence ratings for 505(b)(2) drug products."[124/] In its more specific discussion of this issue, the Agency explains that a follow-on product that contains a different salt than the reference listed drug is a pharmaceutical alternative and not eligible to obtain an "A" therapeutic equivalence rating.[125/]

---

requirement for more than one adequate and well-controlled investigation reflects the need for independent substantiation of experimental results).

122/ Food and Drug Admin., Approved Drug Products with Therapeutic Equivalence Evaluations; Preface (2004) ("Orange Book").

123/ See supra note 3 and accompanying text.

124/ FDA Response to Citizen Petitions filed by Pfizer Inc, Biotechnology Industry Organization, and TorPharm, Docket Nos. 2001P-0323, 2002P-0447, 2003P-0408 (October 14, 2003), at 2.

125/ Id. at 32-33.

As explained in this citizen petition, like different salts, Omnitrop™ does not have the same active ingredient as Genotropin®. Omnitrop™ has a different molecular weight, genetic sequence of recombinant plasmid, master cell bank, and working cell bank than Genotropin® and, as compared to the Genotropin® formulation, does not contain mannitol but rather contains the preservative benzyl alcohol in the diluent. Accordingly, Omnitrop™ properly must be considered a pharmaceutical alternative to Genotropin® and can not be "A" rated. Further, notwithstanding these specific differences between the composition and structural characteristics of Omnitrop™ and Genotropin®, these products can not be determined to be pharmaceutically equivalent because, as discussed above, the available physical and chemical tests for characterizing rhGH do not detect molecular features that can impact product safety and effectiveness.

Moreover, important questions remain about whether critical aspects of rhGH can be adequately quantified and assessed using standard bioequivalence parameters. It is well known that bioequivalence assessments of recombinant proteins, such as rhGH, are confounded by the existence of endogenous, naturally-occurring proteins in human subjects.[126/] Naturally-occurring growth hormone released from the pituitary will therefore confound measurement of plasma rhGH levels that are used for the determination of AUC and C_{max}. Naturally-occurring growth hormone is released in a non-continuous manner, so it is not possible to quantify and correct for the contribution of endogenous protein to the growth hormone measured in blood samples. Because of the inability to correct for the contribution of endogenous growth hormone to concentrations measured in plasma, investigators have concluded that "bioequivalence of endogenous substances conducted with standard procedures in most cases is a useless exercise."[127/]

In addition to the fact that Omnitrop™ can not meet FDA's legal standard for therapeutic equivalence, Pfizer thus has demonstrated compelling scientific and public health reasons why Omnitrop™ should not be "A" rated.

D. Conclusion

FDA must not approve the NDA for Omnitrop™ because: (1) it is illegal and scientifically improper for FDA to rely on, reference, or otherwise use the clinical and manufacturing information establishing the safety and effectiveness of Genotropin® to approve Omnitrop™; (2) the Omnitrop™ data are inadequate to demonstrate the safety/effectiveness and manufacturing requirements for rhGH products; (3) the Omnitrop™ data do not address the important differences between Omnitrop™ and Genotropin®; and (4) it will not serve the therapeutic needs of children

---

126/ See, e.g., V. Blakesley et al., 2004. Are Bioequivalence Studies of Levothyroxine Sodium Formulations in Euthyroid Volunteers Reliable? Thyroid 14(30):191-200; F. Schindel, 2000. Consideration of Endogenous Backgrounds in Pharmacokinetic Analyses: A Simulation Study. European Journal of Clinical Pharmacology 56(9-10):685-8; A. Marzo et al., 2000. Bioequivalence of Endogenous Substances Facing Homeostatic Equilibria: An Example With Potassium. Pharmacological Research 42(6):523-5.

127/ A. Marzo et al., 2000. Bioequivalence of Endogenous Substances Facing Homeostatic Equilibria: An Example With Potassium. Pharmacological Research 42(6):523-5.

and adults requiring growth hormone replacement therapy. Moreover, FDA can not assign "A" therapeutic equivalence ratings to follow-on rhGH products, such as Omnitrop™.

III. Environmental Impact

The actions requested in this Petition are not within any of the categories for which an environmental assessment is required pursuant to 21 C.F.R. § 25.22. Additionally, the actions requested in this petition are exempt from requirement of an environmental assessment pursuant to 21 C.F.R. § 25.24(a)(11).

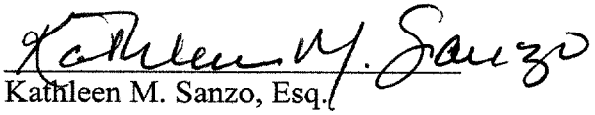
IV. Economic Impact

Information on the economic impact of this proposal can be provided if requested.

V. Certification

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes information and views on which the petition relies, and that it includes representative data and information known to the petitioner that are unfavorable to the petition.

Respectfully Submitted,



Kathleen M. Sanzo, Esq.
Stephen Paul Mahinka, Esq.
Dr. Phoebe Mounts, Esq.
Lawrence S. Ganslaw, Esq.
Morgan, Lewis & Bockius, LLP
1111 Pennsylvania Avenue, N.W.
Washington D.C., 20004
202-739-5209
Counsel for Pfizer Inc

Of Counsel:
Jeffrey B. Chasnow, Esq.
Arnold I. Friede, Esq.
David S. Smith, Esq.
Pfizer Inc
235 East 42nd Street
New York, NY 10017

Attachments